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Discovery Medicine 2026; 38(210): 2140–2152
https://doi.org/10.24976/Discov.Med.202638210.167

The Expression of SSR2 in Pan-Cancer and Its Impact on Patient Survival: A Comprehensive Bioinformatics Analysis

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Submitted: 28 February 2026 Revised: 18 April 2026 Accepted: 24 April 2026 Published: 23 July 2026

Background: Given that aberrant glycosylation acts as a catalyst for tumorigenesis, elucidating Signal Sequence Receptor 2 (SSR2)'s specific patterns is essential to unlock its potential as a prognostic biomarker and clarify its mechanistic role in cancer biology. This study aims to comprehensively characterize the expression landscape and functional significance of SSR2, a pivotal subunit of the oligosaccharyltransferase complex, across normal human tissues and diverse malignancies.

Methods: In this investigation, we utilized advanced bioinformatics resources, including the Human Protein Atlas (HPA), Genotype-Tissue Expression (GTEx), The Cancer Genome Atlas (TCGA), and CPTAC databases, to analyze the expression levels of SSR2 across various human tissues and malignancies. The data were analyzed utilizing the Xiantao academic analysis tool. We performed comparative analyses of SSR2 expression in cancerous and adjacent normal tissues, assessed survival outcomes associated with SSR2 expression levels, and conducted mutation and methylation analyses using cBioPortal and other relevant platforms.

Results: Our findings revealed that SSR2 was predominantly expressed in the pancreas, epididymis, and ovary. Notably, significant differences in SSR2 expression were observed between cancerous and adjacent normal tissues in bladder urothelial carcinoma, breast cancer, and colorectal cancer. High levels of SSR2 correlated with poorer overall survival in adrenocortical carcinoma, esophageal cancer, and clear cell renal carcinoma, while SSR2 expression exhibited a protective effect in ovarian serous cystadenocarcinoma. Furthermore, SSR2 mutations were frequently observed in uterine sarcoma and liver cancer. Methylation analysis identified cg24557248, a CpG site, as a promising prognostic biomarker in clear cell renal carcinoma; increased methylation at this site was linked to improved survival outcomes.

Conclusions: This study emphasizes the complex role of SSR2 in cancer biology, showcasing its potential as both a biomarker and a therapeutic target. Furthermore, the link between SSR2 and tumor immune cell infiltration indicates its role in shaping tumor microenvironments. Future investigations should aim to clarify how SSR2 affects tumor growth and immune regulation, which could lead to innovative therapeutic approaches for cancer treatment.

Keywords: SSR2; pan-cancer; survival analysis; gene mutation; methylation; immune infiltration

Introduction

Cancer remains a leading cause of death worldwide and imposes a heavy financial burden on both patients and society [1]. Nearly one in six deaths worldwide (16.8%) is caused by cancer, and it accounts for about one in four deaths (22.8%) among non-communicable diseases (NCDs) [2]. Currently known treatment methods include surgery, radiotherapy, and chemotherapy. However, these methods are associated with significant side effects, issues with drug resistance, and unsatisfactory survival rates. Therefore, it is essential to investigate the molecular mechanisms of cancer and identify new therapeutic targets. Cancer occurrence and progression are complex processes influenced by genetic, epigenetic, and environmental factors [3].

These elements synergistically drive tumor initiation and metastatic progression. Recently, advances in molecular biology and bioinformatics have enabled researchers to investigate the underlying molecular mechanisms of cancer more comprehensively, with a specific focus on pinpointing critical entities such as receptors and signaling proteins that regulate tumor proliferation and therapeutic resistance [4]. Investigations into these biomolecules offer novel perspectives and identify promising therapeutic targets for early cancer detection and personalized medicine strategies.

Signal Sequence Receptor 2 (SSR2), also known as Translocon-associated protein subunit beta (TRAPβ), is a key membrane protein localized to the endoplasmic reticulum (ER) [5]. As a component of the signal recognition particle (SRP) receptor complex, it plays an indispensable auxiliary role in cotranslational protein translocation, primarily facilitating the recognition of signal sequences in nascent polypeptide chains and aiding their passage through the ER membrane into the lumen. At the molecular level, SSR2 is a transmembrane protein whose precise topology enables stable anchoring in the ER membrane and interaction with other translocon components, such as the Sec61 complex, forming an efficient protein translocation channel. These structural characteristics underpin SSR2's central role in maintaining ER proteostasis and ensuring the proper folding and localization of secretory and membrane proteins. SSR proteins are believed to participate in protein synthesis in eukaryotic cells. Notably, evidence indicates that SSR2 is involved in the unfolded protein response in the endoplasmic reticulum [6]. However, the role of SSR2 in tumor biology remains incompletely understood, and its expression and function across different cancers have attracted increasing research attention. At present, research has found that SSR2 plays a key role in the progression of liver cancer and contributes to drug resistance in gastric cancer through different mechanisms. SSR2 holds potential as a prognostic marker, a therapeutic target, and a target for reversing drug resistance. Further validation of its functionality and clinical feasibility in other types of cancer will be needed [7,8].

This study focuses on the human Signal Sequence Receptor 2 (*SSR2*) gene and its role in various cancers, as its expression pattern is closely related to patient prognosis, while its molecular mechanisms and biological functions remain unclear. This research gap shows the need for the present study. We aim to comprehensively evaluate SSR2's expression, mutations, and methylation patterns, and to explore its relationship with immune infiltration in the tumor microenvironment, thereby clarifying the potential biological functions of SSR2 in cancer progression and treatment. We applied thorough bioinformatics methods in this study, utilizing publicly available databases, such as Human Protein Atlas (HPA), Genotype-Tissue Expression (GTEx), The Cancer Genome Atlas (TCGA), and cBioPortal, to systematically analyze the expression patterns of the *SSR2* gene in various cancers. This approach enables the integration of large-scale transcriptomic and genomic data, providing a more complete understanding of SSR2 expression and its relationship with clinical outcomes across different oncological contexts. This will help uncover the potential functions of SSR2 in cancer progression, assist in the identification of new biomarkers and therapeutic targets, and promote the development of cancer management and personalized treatment strategies.

Methods

Analysis of Organ-Specific Expression

To characterize the expression profile of SSR2 across normal human tissues, we integrated data from the HPA (https://www.proteinatlas.org/) and the GTEx public repository (https://gtexportal.org/home/). Specifically, transcript abundance metrics, quantified as TPM values, were leveraged to delineate the distribution patterns and expression magnitudes of SSR2 within diverse populations. The consensus dataset consists of normalized expression (nTPM) levels for 55 tissue types, created by combining the HPA and GTEx transcriptomics datasets using the internal normalization pipeline. Color-coding is based on tissue groups, with each consisting of tissues that share common functional features. The Kaplan-Meier (KM) method was used to estimate survival rates and plot survival curves for each group, with intergroup comparisons conducted using the Log-rank test.

Cancer Expression Patterns and Pathological Staging Analysis

To comprehensively evaluate SSR2 transcript abundance across diverse malignancies, such as breast, lung, and renal carcinomas, we harmonized datasets derived from (TCGA; https://portal.gdc.cancer.gov/) and the GTEx project. Subsequent statistical computations were executed via the Xiantao analytical platform. Furthermore, using the GEPIA2 interface (http://gepia2.cancer-pku.cn/), we delineated differential SSR2 expression profiles between malignant specimens and their normal counterparts, while simultaneously interrogating potential correlations between transcript levels and pathological tumor staging.

Analysis of Mutations and Methylation

Leveraging the cBioPortal platform, we systematically characterized the mutational landscape of SSR2 across diverse malignancies to determine its prevalence and clinical implications. Concurrently, we integrated CPTAC datasets with the MethSurv platform to rigorously evaluate SSR2 methylation profiles. Collectively, these multiomic analyses were designed to decipher the functional consequences of such genomic and epigenetic aberrations on SSR2-mediated oncogenic mechanisms.

Immune Infiltration Analysis

To elucidate the correlation between SSR2 transcript levels and immune cell infiltration within the tumor microenvironment, we leveraged the TIMER2.0 platform (http://timer.comp-genomics.org/). We quantified infiltration abundances across diverse malignancies by integrating multiple computational deconvolution algorithms, specifically EPIC, MCPcounter, xCell, and TIDE. Our analysis prioritized cancer-associated fibroblasts (CAFs), T lymphocytes, and natural killer (NK) cells, given their pivotal

roles in driving tumor progression and mediating immune escape mechanisms.

Statistical Analysis

Statistical analyses were conducted leveraging the integrated computational modules of established bioinformatics platforms, including TIMER2.0, CIBERSORT, GEPIA2, and cBioPortal. The analytical framework employed diverse statistical approaches, specifically linear regression modeling, partial correlation analysis, and log-rank testing. For comparisons between two groups, normal distribution and homogeneity of variance were first assessed, and either paired or unpaired *t*-tests were applied accordingly. For continuous variables that did not meet the normal distribution assumption, the Wilcoxon rank-sum test was used. To ensure data integrity, all analyses were subjected to tumor purity and corrected for multiple hypothesis testing. A p-value cutoff of <0.05 was considered statistically significant across all assessments. Furthermore, adherence to the platform-specific standard operating protocols was maintained to guarantee methodological rigor and reproducibility.

Results

Expression of SSR2 in Healthy Human Tissues

Analysis of the HPA and GTEx databases showed that SSR2 was widely expressed in healthy human tissues, with the highest levels found in the pancreas, epididymis, and ovary (Fig. 1).

Comparison of SSR2 Protein Expression Levels Across Different Cancers

With the development of modern bioinformatics tools and databases, a comprehensive analysis of the SSR2 protein structure and its expression patterns across different species and cancers was provided in this study. The goal was to reveal its potential biological functions in human health and disease. By utilizing databases such as TCGA, CPTAC, and TCGA_GTEx, researchers have analyzed the SSR2 protein sequence in humans (H. sapiens). Analysis of TCGA (Fig. 2A) (Specific sample size data are shown in **Supplementary Table 1**) and TCGA_GTEx (Fig. 2B) (Specific sample size data are shown in **Supplementary Table 2**) data revealed significant differences in SSR2 expression between cancer tissues and adjacent non-cancerous tissues in several cancers, including urothelial carcinoma (BLCA), invasive breast cancer (BRCA), cholangiocarcinoma (CHOL), and colon cancer (COAD) ($p < 0.05$). Data from the TCGA_GTEx database also showed a similar trend in diffuse large B-cell lymphoma (DLBC). Analysis of the CPTAC database (Fig. 2C) revealed significant differences in SSR2 protein expression between cancer tissues and adjacent non-cancerous tissues in several cancers, including breast, colon, ovarian, clear cell renal cell carcinoma, and endometrial cancers ($p < 0.05$). Furthermore, the study demonstrated that SSR2 expression levels vary significantly across different stages of oral squamous cell carcinoma (Fig. 2D), urothelial carcinoma (Fig. 2E), clear cell renal cell carcinoma (Fig. 2F), and endometrial cancer (Fig. 2G) ($p < 0.05$). The abbreviations for cancer types (e.g., BRCA for breast invasive carcinoma) are detailed in **Supplementary Table 3**.

Exploring How SSR2 Gene Expression Affects Survival in Different Cancer Types

This study used data from the TCGA database to investigate variation in SSR2 protein expression across different cancer types. We further analyzed the relationship between SSR2 expression and survival rates. The study found that patients with high SSR2 levels in adrenocortical carcinoma (ACC), esophageal cancer (ESCA), clear cell renal carcinoma (KIRC), and hepatocellular carcinoma (LIHC) had poorer survival, suggesting that higher SSR2 levels may be associated with worse outcomes in these cancers (Fig. 3A). Conversely, in ovarian serous cystadenocarcinoma (OV), lower SSR2 expression was linked to shorter overall survival. This finding suggests that high SSR2 levels might confer protective effects and improve treatment response. In the disease-specific survival (DSS) analysis (Fig. 3B), higher SSR2 expression was associated with shorter survival in ACC, ESCA, KIRC, kidney papillary cell carcinoma (KIRP), and LIHC. The only exception was lung adenocarcinoma (LUAD), where higher SSR2 expression correlated with longer survival. This result might indicate that the SSR2 protein could have a protective effect in OV and LUAD. Additionally, in the progression-free survival (PFI) analysis, patients with lower SSR2 expression in ACC, ESCA, KIRC, and KIRP showed better progression-free survival (Fig. 3C).

Impact of SSR2 Gene Mutations on Tumor Biology and Prognosis in Various Cancers

Analysis using cBioPortal revealed a high mutation frequency of the *SSR2* gene in cancers such as uterine sarcoma, hepatocellular carcinoma, and cholangiocarcinoma (Fig. 4A). The high incidence of SSR2 mutations in these cancers might suggest its important role in tumorigenesis. Survival analysis revealed no statistically significant differences in overall survival (OS) (Fig. 4C), disease-specific survival (DSS) (Fig. 4D), or progression-free survival (PFS) (Fig. 4E) between patients harboring SSR2 mutations and those without mutations ($p > 0.05$). Analysis of cancer patient samples allowed us to generate a diagram illustrating the location of the R142Q/* missense mutation within the critical TRAPβ domain of the SSR2 protein (Fig. 4B), which may affect protein function and associated cellular processes.

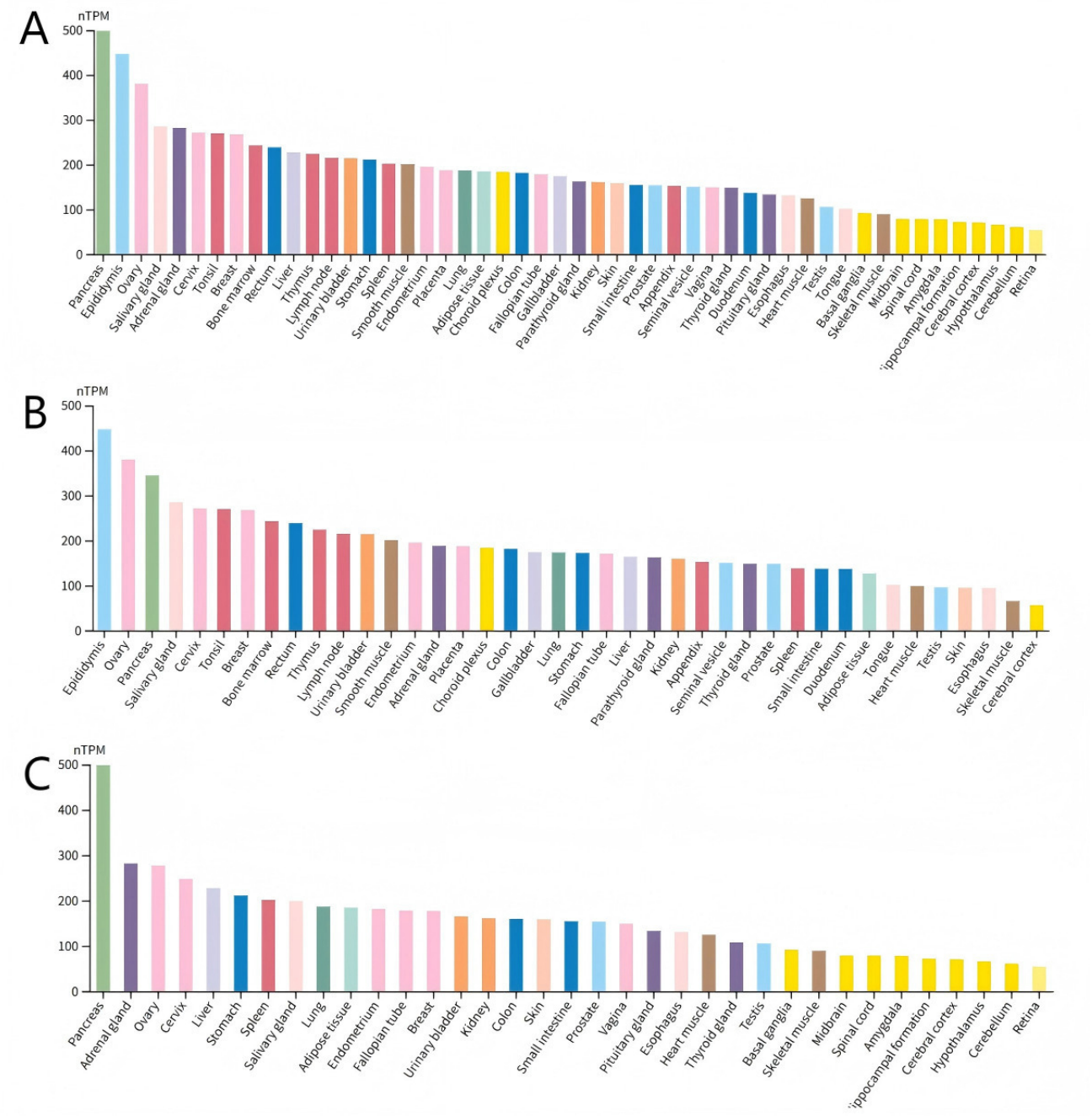

Fig. 1. Expression of SSR2 in normal human tissues. (A) Consensus dataset. (B) HPA dataset. (C) GTEx dataset. SSR2, Signal Sequence Receptor 2; HPA, Human Protein Atlas; GTEx, Genotype-Tissue Expression.

Methylation Patterns of the SSR2 Gene and Their Clinical Significance in KIRC Prognosis

We analyzed the methylation of SSR2 in various cancer types and presented the results as a heatmap, as shown in Fig. 5A. The heatmap revealed significant differences in methylation in KIRC, so we selected KIRC as the research subject. We further analyzed the methylation of SSR2 in KIRC and presented the results as a heatmap, as shown in Fig. 5B. Examination of the SMART database uncovered marked disparities in CpG island methylation intensities when comparing malignant tissues to their adjacent non-tumor counterparts (Fig. 5C) ($p < 0.05$). This unique epigenetic feature is evident in various cancers such as BLCA, BRCA, KIRP, LIHC, PRAD, and UCEC. Upon identifying substantial methylation variations in kidney renal clear cell carcinoma (KIRC), the analysis was further focused on the specific locus cg24557248. The generated heatmap illustrates methylation profiles across numerous KIRC specimens, highlighting cg24557248 as the site with the most pronounced divergence. Notably, methylation status at cg24557248 appears largely independent of demographic variables, including age, sex, clinical stage, and eth-

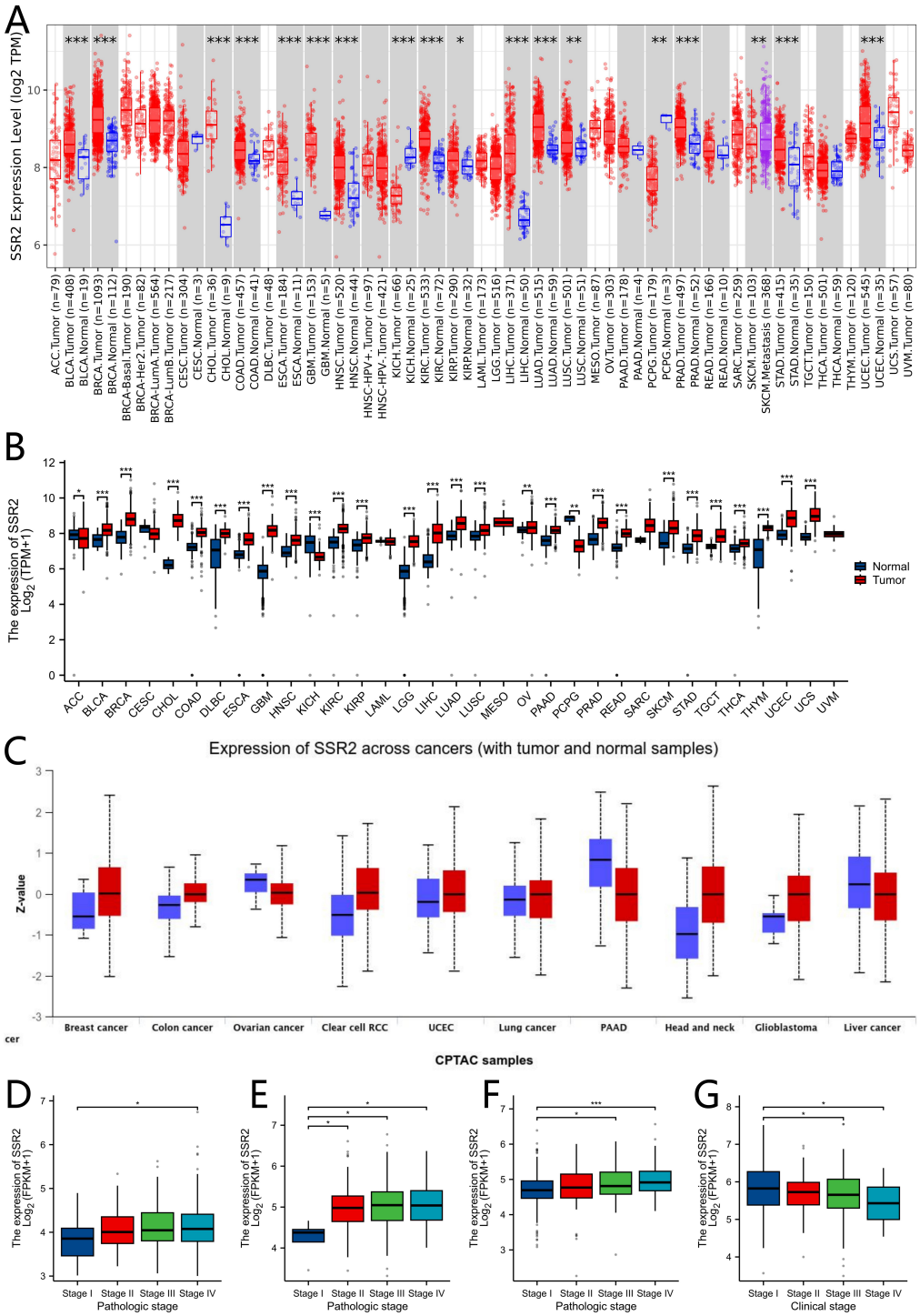

Fig. 2. Analysis of SSR2 protein expression patterns in various cancer types and pathological stages. (A) Using data from the TCGA database, we applied the TIMER2 tool to compare SSR2 expression levels between cancerous and adjacent tissues in different cancers. (B) We analyzed SSR2 expression in cancers such as ACC, BLCA, and BRCA, and included data from the normal control group of the GTEx database. (C) We analyzed the expression distribution of SSR2 protein in specific cancers, including breast cancer, colon cancer, ovarian cancer, clear cell renal cell carcinoma, and endometrial cancer, using CPTAC sample data. (D–G) We analyzed changes in *SSR2* mRNA expression across different stages (I to IV) of oral squamous cell carcinoma, urothelial carcinoma, clear cell renal cell carcinoma, and endometrial cancer using TCGA data. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, NS (Not Significant): $p \geq 0.05$. Abbreviations for all cancer types are defined in **Supplementary Table 3**. TCGA, The Cancer Genome Atlas; ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma.

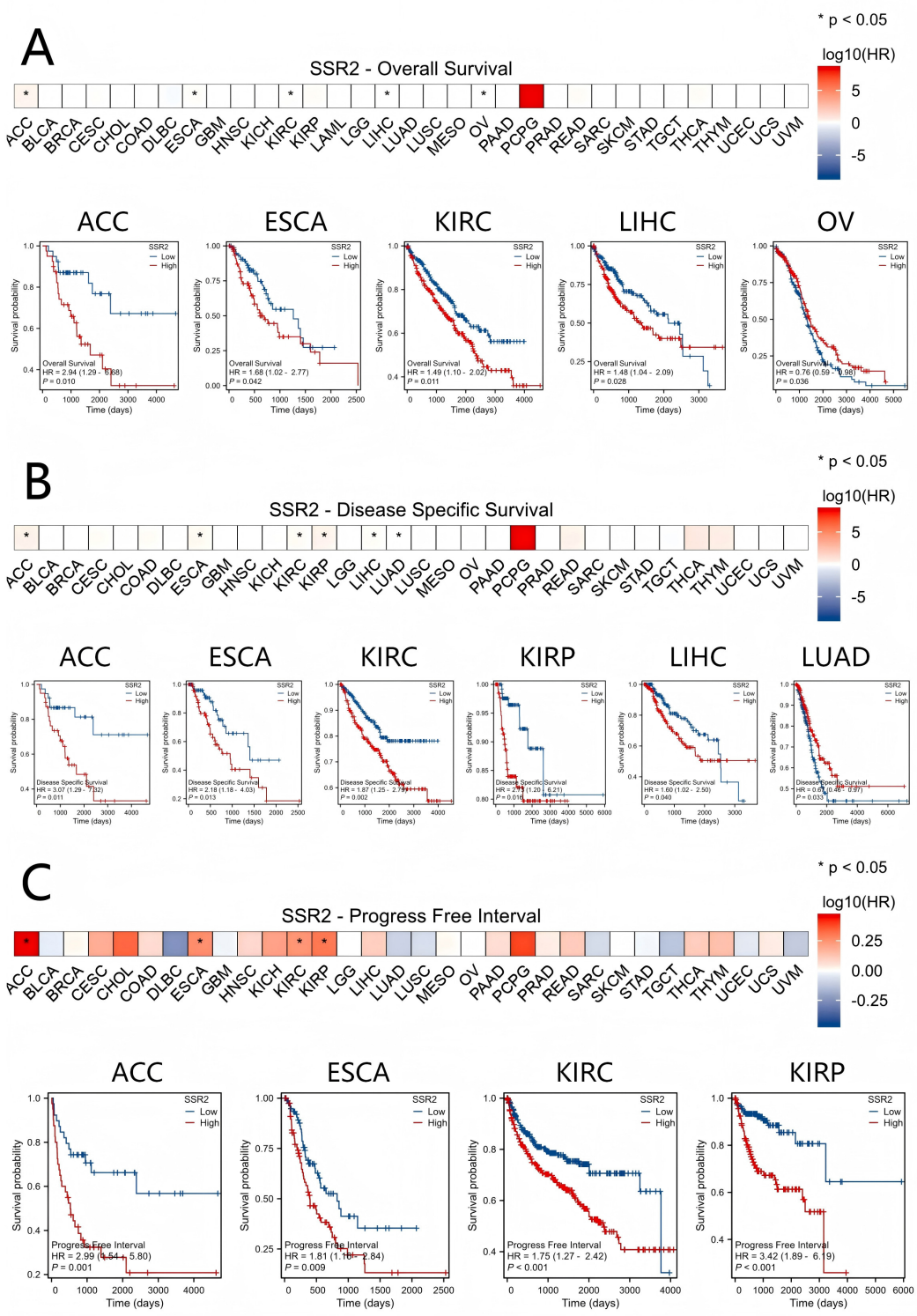

Fig. 3. Expression and survival analysis of the *SSR2* gene across different types of cancer. (A,B) show results based on data from the TCGA database. The GEPIA2 tool was used to analyze the relationship between *SSR2* gene expression levels and overall survival (OS) (A), disease-specific survival (DSS) (B), and progression-free interval (PFI) (C) in patients with various cancers. * $p < 0.05$. Abbreviations for all cancer types are defined in **Supplementary Table 3**.

nicity (Fig. 5D). This observation suggests that methylation dynamics at this locus are primarily regulated by tumor-intrinsic biological mechanisms specific to KIRC rather than host-related factors. We identified the peak of the curve, and the corresponding x-axis value was taken as the optimal cut-off point (β = 0.010) (Fig. 5E). Further-

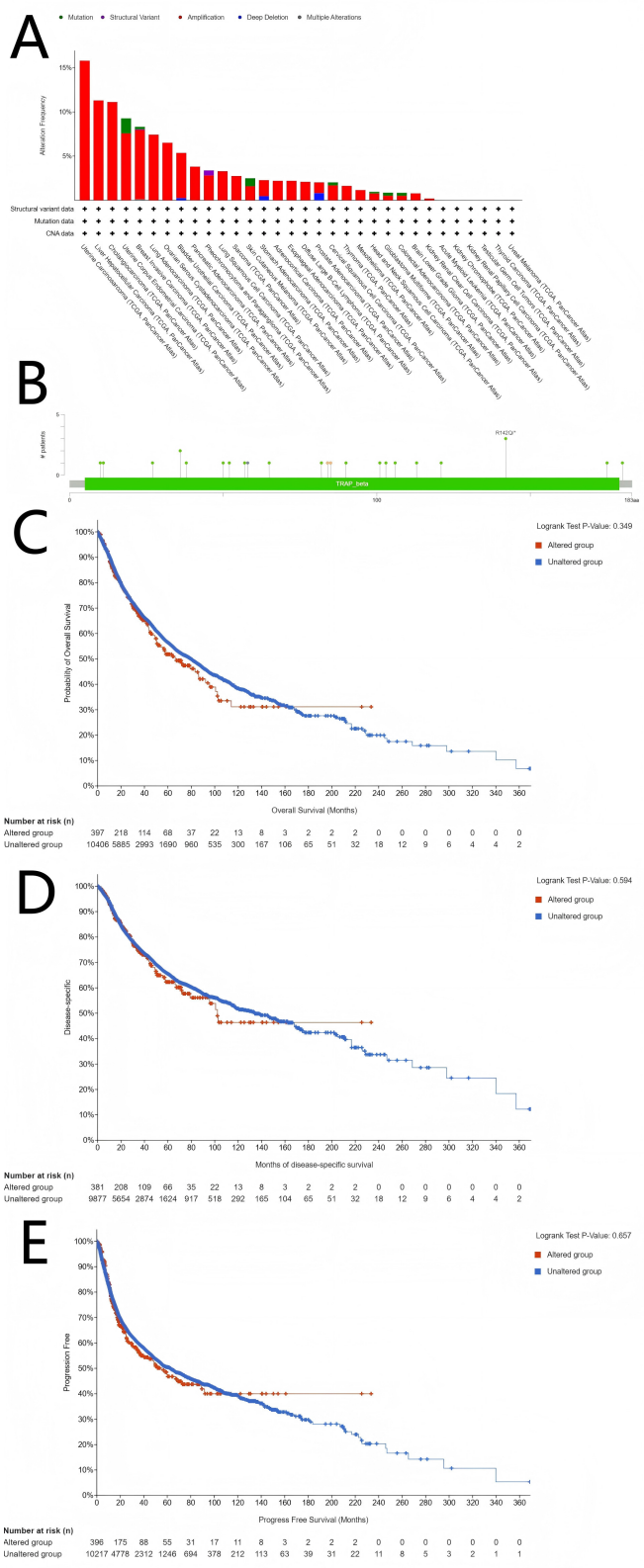

Fig. 4. Analysis of *SSR2* gene mutations in various cancers. (A) Based on the TCGA database, the cBioPortal tool was used to analyze the frequency of *SSR2* gene mutations, including mutations, amplifications, and deep deletions, across various cancers. (B) A schematic diagram shows the R142Q/* missense mutation site in the *SSR2* gene, derived from an analysis of cancer patient samples. Green represents Missense mutation; Gray represents truncating mutation; Yellow represents splice mutation. (C–E) Using TCGA data, the Kaplan-Meier method and Log-rank test compared overall survival (OS) (C), disease-specific survival (DSS) (D), and progression-free survival (PFS) (E) between the mutation and non-mutated groups.

more, Kaplan-Meier survival curves demonstrate that elevated methylation at cg24557248 correlates significantly with prolonged overall survival (Fig. 5F).

Analysis of SSR2 in Tumor Microenvironment Immune Infiltration

This study employed several computational algorithms to investigate the interactions among SSR2, cancer-associated fibroblasts (CAF), and T cell NK cells, thereby revealing the effect of SSR2 on tumor progression. Using the TIMER2.0 platform and algorithms such as EPIC, MCPCOUNTER, XCELL, and TIDE, we initially investigated the role of SSR2 expression in regulating CAF infiltration within the TCGA database (Fig. 6A). Our findings revealed a strong positive correlation between higher SSR2 expression and CAF infiltration across most cancer types, particularly in head and neck squamous cell carcinoma (HNSC) (Fig. 6B), kidney papillary cell carcinoma (KIRP) (Fig. 6C), and testicular germ cell tumors (TGCT) (Fig. 6E). Conversely, in prostate cancer (PRAD) (Fig. 6D), we observed a significant negative correlation between elevated SSR2 expression and CAF infiltration. Subsequently, we examined the relationship between SSR2 expression and T cell/NK cell infiltration (Fig. 6F). Utilizing the XCELL algorithm, we identified notable positive correlations in hepatocellular carcinoma (LIHC) (Fig. 6J), kidney papillary cell carcinoma (KIRP) (Fig. 6I), and ESCA (Fig. 6H), where increased SSR2 levels corresponded with heightened T cell/NK cell infiltration. These results imply that SSR2 may enhance anti-tumor effects by boosting T cell/NK cell activity in these specific tumors. However, in uterine sarcoma (UCS) (Fig. 6K) and ACC (Fig. 6G), high SSR2 expression was significantly negatively correlated with T cell/NK cell infiltration, indicating that SSR2 might facilitate tumor progression by inhibiting the immune function of these cells.

Discussion

This study found that the *SSR2* gene is expressed at the highest levels in the human pancreas, epididymis, and ovary. Further analysis showed that SSR2 is highly expressed in cancers such as bladder urothelial carcinoma (BLCA), invasive breast cancer (BRCA), cholangiocarcinoma (CHOL), colon cancer (COAD), and diffuse large B-cell lymphoma (DLBC). The varying expression levels of SSR2 in cancer tissues highlight its importance in tumor biology. These findings are statistically significant and indicate that SSR2 could be a valuable biomarker for early cancer detection and disease monitoring. Previous studies have shown higher SSR2 expression in hepatocellular carcinoma [9,10] tissues compared to adjacent non-cancerous tissues, consistent with our findings.

Survival analysis indicates that high expression levels of SSR2 are linked to poorer overall survival rates in patients with ACC, ESCA, and clear cell renal carcinoma (KIRC). Conversely, lower SSR2 expression is associated with worse survival outcomes in patients suffering from serous cystadenocarcinoma (OV). These observations underscore the prognostic significance of SSR2, suggesting its potential role in guiding personalized treatment strategies. Currently, existing clinical data suggest that in hepatocellular carcinoma (HCC), patients with higher expression levels of SSR2 have poorer survival [9]. Additionally, high expression of SSR2 is also associated with adverse responses to the first-line targeted drug Sorafenib and poor clinical outcomes in liver cancer patients [11]. The opposite effects of SSR2 on survival across different cancer types highlight its complex biological functions and underscore the need for further investigation into the underlying mechanisms. Notably, significant variations in SSR2 expression have been observed across different stages of oral squamous cell carcinoma, urothelial carcinoma, clear cell renal carcinoma, and endometrial carcinoma. Previous research has confirmed a positive correlation between high SSR2 expression and factors such as capsule invasion and tumor grading in hepatocellular carcinoma [12]. However, there remains a gap in the literature regarding the exploration of SSR2's relationship with clinicopathological features or survival outcomes in other cancer types.

Analysis of SSR2 mutations has revealed a high frequency of alterations in uterine sarcoma, hepatocellular carcinoma, and cholangiocarcinoma. The primary type of mutation identified is gene amplification, with the most common missense mutation occurring at the R142Q site. These findings suggest a potential connection between SSR2 mutations and tumor development. However, survival analysis shows no significant differences in outcomes between patients with SSR2 mutations and those without, indicating that while these mutations are prevalent, they may not have a direct impact on patient prognosis. Nonetheless, mutations in critical domains of SSR2 could disrupt its normal function and contribute to tumorigenesis, supporting the idea of developing targeted therapies against SSR2 for affected patients. Gene amplification is known to promote tumor cell growth and invasiveness. For instance, experimental studies have shown that inhibiting ADAR1 expression can reduce these aggressive phenotypes, while overexpression can enhance them, suggesting that amplification directly contributes to tumorigenesis. Similarly, in bladder cancer, amplifications of oncogenes such as int-2 and erbB-2 are linked to highly malignant tumors, potentially accelerating tumor progression by disrupting genomic stability and promoting cell proliferation. However, to date, no studies have conclusively demonstrated that *SSR2* gene amplification directly promotes tumor cell proliferation. Multiple studies have indicated that gene mutations have an impact on the progression and survival prognosis of various cancers, such as endometrial cancer [13], colorectal cancer [14–16]. For example, mutations in genes such as

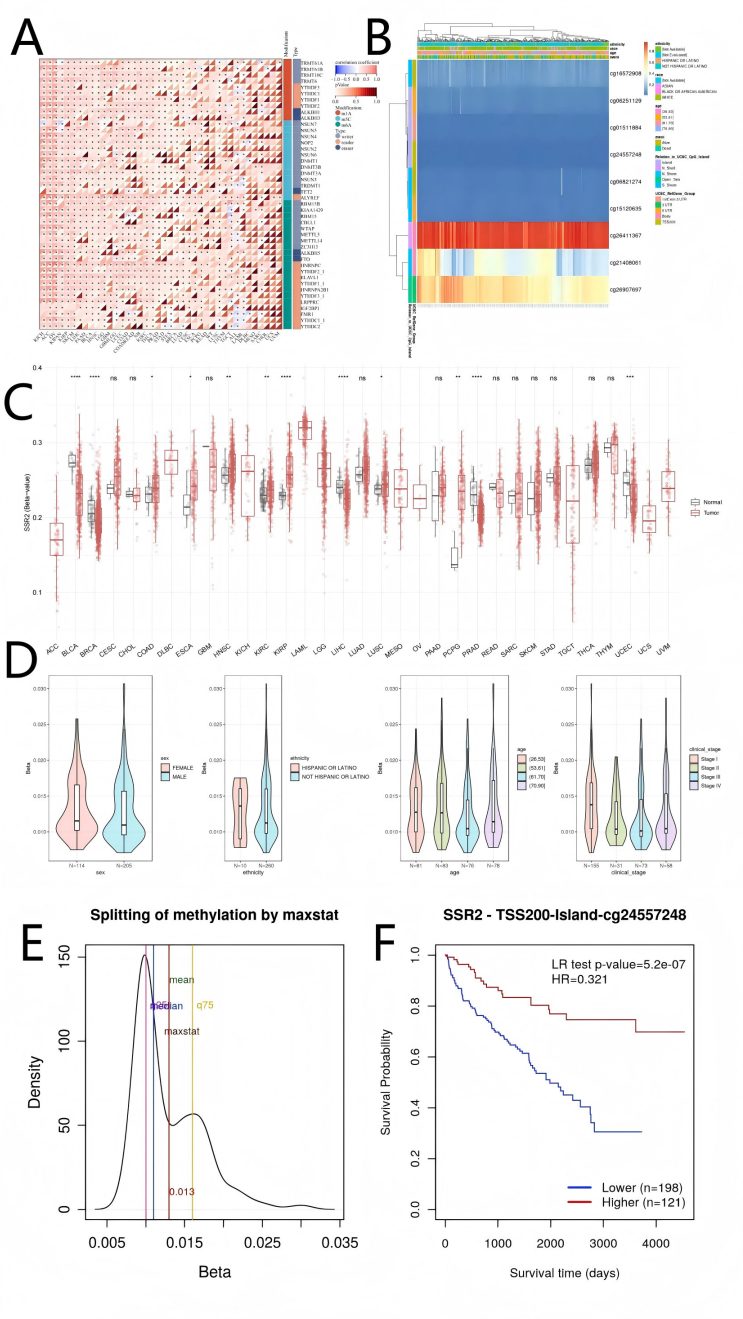

Fig. 5. Analysis of *SSR2* gene methylation levels and their biological significance in kidney clear cell carcinoma (KIRC). The following sections describe the findings on *SSR2* gene methylation. (A) The methylation status of the *SSR2* gene across different cancer types was analyzed using the MethSuv tool and shown as a heatmap. (B) Methylation heatmap specifically for the *SSR2* gene in KIRC. (C) CpG (Cytosine-phosphate-Guanine) cluster methylation values for various cancer types (SMART database). (D) Comparison of *SSR2* gene methylation levels across genders, ethnicities, age groups, and clinical stages using the MethSuv tool. (E) The methylation cutoff point was determined using the maxstat method. (F) Survival analysis based on methylation at the cg24557248 locus was performed using the Kaplan-Meier method. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, NS (Not Significant): $p \geq 0.05$. Abbreviations for all cancer types are defined in **Supplementary Table 3**.

RAS, BRAF, mismatch repair (MMR) genes, TP53, and SMAD4 have prognostic value in patients with colorectal cancer liver metastasis [16].

This study investigates the methylation patterns of the *SSR2* gene in kidney renal clear cell carcinoma (KIRC) and examines their potential implications for cancer prognosis. Our findings reveal a significant difference in methylation levels at the cg24557248 site when comparing cancerous tissues to adjacent non-cancerous tissues, a result that is corroborated by data from the SMART database. The

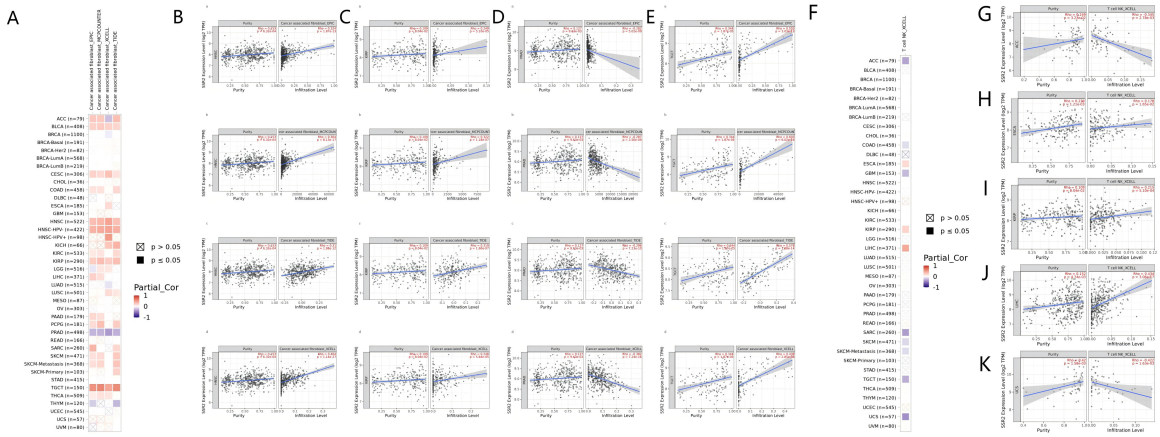

Fig. 6. Analysis of the correlation between *SSR2* gene expression and immune cell infiltration in the tumor microenvironment. (A) Using the TCGA database, the correlation between *SSR2* gene expression and cancer-associated fibroblast (CAF) infiltration levels was analyzed. Four algorithms—EPIC, MCPCOUNTER, XCELL, and TIDE—within the TIMER 2.0 tool were applied for this analysis. (B–E) Scatter plots illustrated the correlation between *SSR2* gene expression and CAF infiltration levels in four cancer types: head and neck squamous cell carcinoma (B), kidney papillary cell carcinoma (C), prostate cancer (D), and testicular germ cell tumors (E), using the four algorithms mentioned above. (F) We analyzed the correlation between *SSR2* gene expression and natural killer (NK) cell infiltration using the XCELL algorithm. (G–K) Scatter plots displayed the relationship between *SSR2* gene expression and NK cell infiltration levels in adrenocortical carcinoma (G), esophageal cancer (H), kidney papillary cell carcinoma (I), hepatocellular carcinoma (J), and uterine sarcoma (K), with correlations assessed by the XCELL algorithm. Abbreviations for all cancer types are defined in **Supplementary Table 3**.

notable change in methylation at the cg24557248 site in KIRC samples suggests its potential as a valuable prognostic biomarker, as evidenced by Kaplan-Meier survival curves analysis, indicating that higher methylation levels at this site are linked to longer survival rates. This relationship underscores the possibility that the methylation status at cg24557248 could influence clinical outcomes independently of demographic variables such as age, gender, clinical stage, and ethnicity. This suggests that the regulation of methylation at the cg24557248 site may be predominantly influenced by tumor-specific biological mechanisms in KIRC. Additionally, previous research has shown that promoter methylation of genes like sFRP1, MLH1, and RASSF1A in colorectal cancer can inhibit gene expression and potentially disrupt DNA repair and apoptosis pathways, thereby increasing tumor cell proliferation and invasiveness. Numerous studies have shown that the methylation levels of oncogenes differ in tumor tissues and are correlated with tumor-related biological behaviors. For instance, the methylation levels of multiple genes, including SP1, were measured in tumor and paired normal tissues from 50 patients. The results indicated that the methylation level of the SP1 gene in tumor DNA was consistently higher than in normal tissues across all patients and different clinical subgroups (such as different tumor sites and stages) [17]. Moreover, in cases where histological classification is challenging, such as thyroid follicular-patterned tumors, machine learning models based on DNA methylation profiles can effectively distinguish between benign and malignant tumor subtypes [18]. Additionally, in the analyzed breast cancer tumor tissues, the proportion of abnormal methylation in the RASSF1A gene promoter was very high (93%), and even in the corresponding non-tumor (adjacent) tissues, a high proportion of methylation (67%) was observed. By correlating methylation status with clinicopathological characteristics, the study concluded that promoter methylation of the RASSF1A gene is significantly associated with larger tumor volume and higher tumor histological grade [19].

This contrasts with our conclusion that *SSR2* gene methylation leads to longer survival in KIRC patients, and currently, no studies indicate that *SSR2* gene methylation patterns affect tumor cell proliferation and progression. The TRAP complex preferentially binds misfolded proteins, such as NHK, during ER-associated degradation (ERAD), rather than normally folded proteins. When the TRAP function is lost, abnormal proteins are degraded less efficiently, leading to increased burden and stress on the endoplasmic reticulum [20].

Furthermore, the investigation of the immune microenvironment reveals a complex relationship between SSR2 expression and immune cell infiltration. This relationship is especially notable with cancer-associated fibroblasts (CAFs) and T cells/NK cells. Tumor-associated fibroblasts (CAFs) are part of the tumor microenvironment and promote cancer cell growth and invasion by secreting various growth factors and cytokines. We used various computational methods, including TIMER2.0 and XCELL,

to identify a strong positive correlation between elevated SSR2 expression and CAF infiltration across multiple cancer types, especially HNSC, KIRP, and TGCT. Existing evidence [21] has shown that the crosstalk between CAFs and cancer cells creates a favorable microenvironment for tumor progression through epithelial-mesenchymal transition. In contrast, the negative correlation observed in PRAD suggests that SSR2 may contribute to reducing immune evasion. Additionally, a positive association was observed between SSR2 expression and T cell/NK cell infiltration in LIHC, KIRP, and ESCA. Research has demonstrated [22] that in lung cancer and lymphoma, NK cells expressing high levels of immune checkpoint molecules generate an immunosuppressive microenvironment by inhibiting dendritic cells and CD8+ T cell activity, which leads to treatment resistance. Similarly, in hepatocellular carcinoma, the infiltration of exhausted T cells and NK cells is positively correlated with tumor invasiveness. This leads to poorer survival rates due to decreased cytotoxic function and enhanced immune evasion mechanisms [23]. In esophageal cancer, the accumulation of exhausted T cells and NK cells is associated with resistance to PD-1 inhibitors [24]. Additionally, in endometrial cancer, dysfunctional NK cells enhance immune suppression through interactions with macrophages, potentially counteracting anti-tumor effects [25]. CAFs, as one of the most abundant and critical stromal cell components in the tumor microenvironment (TME), profoundly influence the occurrence and development of cancer through various complex mechanisms [26]. CAFs actively remodel the stroma surrounding tumors by depositing extracellular matrix (ECM) components and secreting matrix-degrading enzymes [27]. This leads to tumor stromal fibrosis (desmoplastic reaction), creating a stiffer physical and biochemical environment more conducive to tumor progression and metastasis [28]. Natural Killer T (NKT) cells are a unique subset of T lymphocytes, characterized by their co-expression of receptors or surface markers typically associated with T cells and NK cells. In patients with various cancers (including hepatocellular carcinoma, breast cancer, and ovarian cancer), the number of NKT cells in peripheral blood and tumor tissues is often reduced, and their functions, such as cytokine production (e.g., IFN-γ) and cytotoxicity, are impaired [29]. This functional exhaustion is associated with cancer progression and poor prognosis. Current studies have confirmed that the "cytotoxic activity" of NKT cells is directly linked to anti-tumor immune responses [30].

The negative correlations observed in UCS and ACC suggest potential immunosuppressive roles in certain tumor types. However, no experimental evidence shows that the *SSR2* gene drives tumor progression by reshaping the tumor microenvironment and enhancing immune evasion via regulating CAFs, T cells, and NK cells.

In conclusion, our comprehensive analysis of SSR2 across various cancer types has shed light on its expression patterns and prognostic significance, emphasizing its potential as a therapeutic target. However, some limitations must be acknowledged. Firstly, our study predominantly utilized public databases, which may lead to underrepresentation of certain cancer biopsy samples or patient populations. Furthermore, our findings were based on bioinformatics predictions that necessitate experimental validation to confirm SSR2's functional roles. Therefore, future research should prioritize the experimental validation of these results and delve into the mechanisms by which SSR2 operates in cancer biology. This approach will not only enhance our understanding of SSR2 but also facilitate the development of its clinical utility in cancer treatment, ultimately contributing to the advancement of personalized therapeutic strategies.

Conclusions

This study reveals significant variations in SSR2 expression, mutations, and methylation across various cancers, suggesting that SSR2 holds promise as a target for both diagnosis and treatment. The differences in SSR2 expression among different cancers indicate that this receptor may play diverse roles in tumor progression. SSR2 interacts within the TME and may influence immune regulation and tumor dynamics, with particularly notable effects on fibroblasts and T/NK cells. These findings provide new insights into the multifunctional role of SSR2, which could optimize cancer diagnosis and treatment strategies, paving the way for future studies focused on its underlying mechanisms and clinical applications in cancer. While analyses from multiple public databases have yielded positive results, it is crucial for future research to include experimental validation and clinical trials to confirm these bioinformatics findings and support their application in precision medicine. Subsequent studies should further elucidate SSR2's mechanisms of action across various tumors, validate its effectiveness as a biomarker, and accelerate the development of safe and effective targeted therapeutic strategies.

Availability of Data and Materials

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Author Contributions

YHH and GPS were responsible for the study design. YX, WJJ, JTL, and LLF were responsible for study implementation. YHH and YX were responsible for data collection and analysis. YHH and YX participated in drafting the manuscript. All authors contributed to the important editorial changes in the manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

We thank the Gene Expression Omnibus (GEO), The Cancer Genome Atlas (TCGA) Database for sharing a large amount of data, TIMER2.0, CIBERSORT, GEPIA2 and cBioPortal. We would also like to express our gratitude to Xiantao Academic for their support in data analysis.

Funding

This study was supported by the General Project of the National Natural Science Foundation of China (Project No. 82072751).

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.24976/Discov.Med.202638210.167.

References

[1] Tarekegn TB, Ashagrie G, Kassaw AT, Gebrie D, Girmaw F. Economic Burden and Cost-Effectiveness of Cancer Care in Ethiopia: A Systematic Review. Value in Health Regional Issues. 2026; 52: 101515. https://doi.org/10.1016/j.vhri.2025.101515.

[2] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, *et al*. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2024; 74: 229–263. https://doi.org/10.3322/caac.21834.

[3] Colin F, Schauer K, Hamiche A, Martineau P, Borg JP, Bednar J, *et al*. The NANOTUMOR consortium - Towards the Tumor Cell Atlas. Biology of the Cell. 2021; 113: 272–280. https://doi.org/10.1111/boc.202000135.

[4] Zhao Y, Hou J, Liu Y, Xu J, Guo Y. An arabinose-rich heteropolysaccharide isolated from Belamcanda chinensis (L.) DC treats liver cancer by targeting FAK and activating CD40. Carbohydrate Polymers. 2024; 331: 121831. https://doi.org/10.1016/j.carbpol.2024.121831.

[5] Amarakoon D, Peng J, Wei CI, Lee SH. Knockdown of translocon-associated protein subunit beta (TRAPβ) stimulates cell cycle arrest and apoptosis in human colorectal cancer cells. Biochimica et Biophysica Acta. Molecular Cell Research. 2025; 1872: 120057. https://doi.org/10.1016/j.bbamcr.2025.120057.

[6] Garg B, Pathria G, Wagner C, Maurer M, Wagner SN. Signal Sequence Receptor 2 is required for survival of human melanoma cells as part of an unfolded protein response to endoplasmic reticulum stress. Mutagenesis. 2016; 31: 573–582. https://doi.org/10.1093/mutage/gew023.

[7] Huang S, Zhong W, Shi Z, Wang K, Jin H, Zhang Z, *et al*. Overexpression of signal sequence receptor γ predicts poor survival in patients with hepatocellular carcinoma. Human Pathology. 2018; 81: 47–54. https://doi.org/10.1016/j.humpath.2018.06.014.

[8] Liu Y, Cao J, Pu YS, Ma Y, Wu M, Wang JH. RP11-874J12.4, a novel lncRNA, confers chemoresistance in human gastric cancer cells by sponging miR-3972 and upregulating SSR2 expression. American Journal of Translational Research. 2021; 13: 5892–5910.

[9] Chen F, Chen, Wang J, Zhang S, Chen M, Zhang X, *et al*. Overexpression of SSR2 promotes proliferation of liver cancer cells and predicts prognosis of patients with hepatocellular carcinoma. Journal of Cellular and Molecular Medicine. 2022; 26: 3169–3182. https://doi.org/10.1111/jcmm.17314.

[10] Hernandez Vargas S, Aghaamiri S, Adams JT, Bateman TM, Acidi B, Ghosh SC, *et al*. Somatostatin Receptor 2 Overexpression in Hepatocellular Carcinoma: Implications for Cancer Biology and Therapeutic Applications. Current Oncology. 2025; 32: 512. https://doi.org/10.3390/curroncol32090512.

[11] Song Z, Zhou M, Song X, Jia H, Yang X. SSR2 Promotes Sorafenib Resistance Via Interacting with GPX4 to Inhibit Ferroptosis. Current Molecular Medicine. 2026. https://doi.org/10.2174/0115665240405981251201125139. (online ahead of print)

[12] Hong X, Luo H, Zhu G, Guan X, Jia Y, Yu H, *et al*. SSR2 overexpression associates with tumorigenesis and metastasis of Hepatocellular Carcinoma through modulating EMT. Journal of Cancer. 2020; 11: 5578–5587. https://doi.org/10.7150/jca.44788.

[13] Shen Q, Tian C, Luo X, Yang F, Jiang P, Zheng Y. PIK3CA Somatic Mutations Are Associated With Lymph Node Metastasis in Endometrial Cancer. Journal of Sichuan University. Medical Science Edition. 2025; 56: 434–441. https://doi.org/10.12182/20250360106. (In Chinese)

[14] Lin PC, Yeh YM, Chan RH, Lin BW, Chen PC, Pan CC, *et al*. Sequential and co-occurring DNA damage response genetic mutations impact survival in stage III colorectal cancer patients receiving adjuvant oxaliplatin-based chemotherapy. BMC Cancer. 2021; 21: 217. https://doi.org/10.1186/s12885-021-07926-1.

[15] Shi Y, Baral S, Zhang Y, Jiang Y, Li R, Zhang Y, *et al*. Transcriptional regulation of GPSM2 by ZNF263 in colorectal cancer: implications for tumor aggressiveness. Acta Biochimica et Biophysica Sinica. 2026. https://doi.org/10.3724/abbs.2025181. (online ahead of print)

[16] Wang J, Botvinov J, Bhatt AJ, Beyer K, Kreis ME, Adam M, *et al*. Somatic Mutations in Surgically Treated Colorectal Liver Metastases: An Overview. Cells. 2024; 13: 679. https://doi.org/10.3390/cells13080679.

[17] Jumaniyazova E, Aghajanyan A, Kurevlev S, Tskhovrebova L, Makarov A, Gordon K, *et al*. SP1 Gene Methylation in Head and Neck Squamous Cell Cancer in HPV-Negative Patients. Genes. 2024; 15: 281. https://doi.org/10.3390/genes15030281.

[18] Marczyk VR, Recamonde-Mendoza M, Maia AL, Goemann IM. Classification of Thyroid Tumors Based on DNA Methylation Patterns. Thyroid. 2023; 33: 1090–1099. https://doi.org/10.1089/thy.2023.0074.

[19] Gupta V, Agarwal P, Deshpande P. Impact of RASSF1A gene methylation on clinico-pathological features of tumor and non-tumor tissue of breast cancer. Annals of Diagnostic Pathology. 2021; 52: 151722. https://doi.org/10.1016/j.anndiagpath.2021.151722.

[20] Lee J, Manon V, Chen J. Nucleotide-dependent conformational changes direct peptide export by the transporter associated with antigen processing. Immunity. 2025; 58: 2166–2175.e4. https://doi.org/10.1016/j.immuni.2025.08.003.

[21] Wang H, Liang Y, Liu Z, Zhang R, Chao J, Wang M, *et al*. POSTN$^+$ cancer-associated fibroblasts determine the efficacy of immunotherapy in hepatocellular carcinoma. Journal for Im-

munotherapy of Cancer. 2024; 12: e008721. https://doi.org/10.1136/jitc-2023-008721.

[22] Russick J, Joubert PE, Gillard-Bocquet M, Torset C, Meylan M, Petitprez F, *et al*. Natural killer cells in the human lung tumor microenvironment display immune inhibitory functions. Journal for Immunotherapy of Cancer. 2020; 8: e001054. https://doi.org/10.1136/jitc-2020-001054.

[23] Chew V, Lai L, Pan L, Lim CJ, Li J, Ong R, *et al*. Delineation of an immunosuppressive gradient in hepatocellular carcinoma using high-dimensional proteomic and transcriptomic analyses. Proceedings of the National Academy of Sciences of the United States of America. 2017; 114: E5900–E5909. https://doi.org/10.1073/pnas.1706559114.

[24] Zheng Y, Chen Z, Han Y, Han L, Zou X, Zhou B, *et al*. Immune suppressive landscape in the human esophageal squamous cell carcinoma microenvironment. Nature Communications. 2020; 11: 6268. https://doi.org/10.1038/s41467-020-20019-0.

[25] Shi W, Wu W, Wang J, Meng X. Single-cell transcriptomics reveals comprehensive microenvironment and highlights the dysfuntional state of NK cells in endometrioid carcinoma. Medicine. 2024; 103: e37555. https://doi.org/10.1097/MD.0000000000037555.

[26] Jia H, Chen X, Zhang L, Chen M. Cancer associated fibroblasts in cancer development and therapy. Journal of Hematology & Oncology. 2025; 18: 36. https://doi.org/10.1186/s13045-025-01688-0.

[27] Wright K, Ly T, Kriet M, Czirok A, Thomas SM. Cancer-Associated Fibroblasts: Master Tumor Microenvironment Modifiers. Cancers. 2023; 15: 1899. https://doi.org/10.3390/cancers15061899.

[28] Peiffer R, Boumahd Y, Gullo C, Crake R, Letellier E, Bellahcène A, *et al*. Cancer-Associated Fibroblast Diversity Shapes Tumor Metabolism in Pancreatic Cancer. Cancers. 2022; 15: 61. https://doi.org/10.3390/cancers15010061.

[29] Papanastasatou M, Gioulbasani M, Nakou E, Galaras A, Rubio-Tomás T, Talianidis I, *et al*. Dual regulatory role of natural killer T cells during development of hepatocellular carcinoma. Communications Biology. 2025; 8: 1478. https://doi.org/10.1038/s42003-025-08872-5.

[30] Du Y, Lan T, Liu M, Wu W, Ma J. Facilitation of natural killer T-cell cytotoxic activity in uterine sarcoma via the *CKS2-PI3K-AKT-MICA* axis. Translational Cancer Research. 2025; 14: 5045–5058. https://doi.org/10.21037/tcr-2025-1405.